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*Brief report to Blood*

# Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African-American and White veterans in the U.S.

**Short title:** MGUS and multiple myeloma in African-Americans and Whites

**Scientific heading:** Neoplasia

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**ABSTRACT**

The age-adjusted incidence of multiple myeloma (MM) is 2-fold higher in African-Americans than in Whites. A few small studies have reported a higher prevalence of monoclonal gammopathy of undetermined significance (MGUS) in African-Americans versus Whites. Etiological factors for MGUS and determinants for transformation of MGUS to MM are unknown. We quantified the prevalence of MGUS and subsequent risk of MM among 4 million African-American and White male veterans admitted to VA hospitals. The age-adjusted prevalence-ratio of MGUS in African-Americans compared to Whites was 3.0 (2.7-3.3 95%CI). Among 2,046 MGUS cases, the estimated cumulative risk of MM during the first 10 years of follow-up was similar (P=0.37) for African-Americans (17%) and Whites (15%). In the largest study to date, we suggest that the excess risk of MM in African-Americans results from an increase in risk of MGUS rather than an increased risk of progression from MGUS to MM.

## INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy morphologically characterized by a monoclonal proliferation of plasma cells in the bone marrow. In contrast with the Caucasian predominance of most hematopoietic neoplasms, age-adjusted incidence of MM is 2-fold higher in African-Americans (9.5 per 100,000 per year) than in Whites (4.1 per 100,000 per year) (http://seer.cancer.gov). The basis for this race-related difference is unknown.

Monoclonal gammopathy of undetermined significance (MGUS), a benign disorder with a strikingly elevated monoclonal immunoglobulin of <3 grams/deciliter in individuals lacking evidence of MM or other lymphoproliferative malignancies, often precedes MM. A screening study conducted in the 1960s in Sweden demonstrated MGUS prevalence of 0.1-0.2% in persons aged 30-49 years, 1.1-2.0% in those 50-79 years old, and 5.7% in those 80-89 years old [1]. Long-term follow-up of patients with MGUS reveals a 1-3% annual risk of developing MM, or, to a lesser extent, other lymphoproliferative malignancies [2]. Although investigators have recently described potential models of pathogenesis of MGUS and MM, it is unknown whether MGUS precedes all cases of MM or if MM can arise de novo without preceding MGUS. [3,4]

Etiological factors for MGUS and determinants for transformation of MGUS to MM are unknown, but data on the prevalence and progression of MGUS and MM according to race may provide clues to etiology. For example, if the prevalence ratio for MGUS parallels the incidence ratio for MM according to race and the probability of progression to MM is the same in both races; better understanding of the exogenous and genetic risk factors for MGUS would be a priority in order to explain the racial disparity. If however,

the racial differences result from a more rapid rate of progression from MGUS to MM in African-Americans compared to Whites, the focus would move to factors that influence progression. A few small studies have reported a higher prevalence of MGUS in African-Americans compared to Whites. [5-7] The objective of the present study was to quantify and compare the prevalence of MGUS and risk of MM following MGUS among African-Americans and Whites using data from the largest study to date.

## MATERIALS AND METHODS

### Hospitals, patients and outcomes

The cohort was identified from discharge records for inpatient hospitalizations at 142 nationwide U.S. Veterans Affairs (VA) hospitals between October 1, 1980 and September 30, 1996. The target population for calculation of MGUS prevalence included all African-American (N=749,020) and White (N=3,248,795) veterans hospitalized at least once at age 18 or older. MGUS cases were patients from the eligible population with an ICD-9 discharge diagnosis of 273.1 (Table 1). For estimating risk of malignancy, all subjects without a prior discharge diagnosis of malignancy were followed from one year after index hospital discharge (MGUS diagnosis for MGUS cases, and first discharge for any reason for all others) until the diagnosis of a first malignancy, death, or the end of the observation period (September 30, 1996), whichever came first. Dates of death were ascertained from record linkage to Social Security Administration mortality files. The length of the time period for progression to MM was estimated by subtracting the date of discharge for the first hospitalization listing a discharge diagnosis of MGUS from the date of discharge for the first hospitalization listing a discharge diagnosis of MM. Approval was obtained from the NIH institutional review board for these studies. Informed consent was waived because we had no contact with study subjects.

### Statistical methods

Age-adjusted prevalence rates were directly standardized to the year 2000 U.S. standard population. Using the Kaplan-Meier procedure, we calculated the cumulative probability of developing MM among MGUS cases according to race, testing for

statistical significance using the Wilcoxon-test appropriate for censored data. Cox proportional hazards model was applied. Poisson regression was used for analyses comparing risk for MM among MGUS versus non-MGUS cohorts.

## RESULTS AND DISCUSSION

### Age-adjusted prevalence-rates for MGUS

We identified 734 cases of MGUS in African-Americans and 1,312 in Whites (Table 1). The age-adjusted prevalence-rate for MGUS was 3.0-fold (2.7-3.3 95% CI) higher in African-Americans than in Whites.

### Risk of multiple myeloma subsequent to MGUS

Among MGUS cases, the estimated cumulative risk of developing MM during the first 10 years of follow-up was similar (Wilcoxon-test P=0.37) for African-Americans (17%) and Whites (15%) (Figure 1). The relative risk (RR) of MM for African-Americans (relative to Whites) was 1.22 (0.91-1.65, 95% CI), the estimate did not change during each quartile of study-period and was similar for each age group at MGUS diagnosis. As expected, the risk of developing MM among all MGUS (versus other than MGUS) cases was very high (RR=89.1; 74.7-106.3, 95% CI).

An increased prevalence of MGUS in African-Americans (vs. Whites) has been reported in three previous studies of 44 [5], 86 [6], and 106 [7] MGUS cases, respectively. The strength of the current study includes its substantially larger size (N=2,046) in a patient population with relatively stable and standardized access to medical care, that is provided to U.S. veterans independent of socioeconomic status. In addition, patients were followed for intervals as long as 16 years subsequent to MGUS. Limitations include the lack of information about demographic, clinical, laboratory or biomarker information for individual patients in the database. Identification of the cohort from discharge diagnoses,

rather than from screening, is likely to have led to under-ascertainment of MGUS in the hospitalized population studied. Because MGUS is generally asymptomatic, it is not surprising that the prevalence in the U.S. VA hospitals is lower than the prevalence of MGUS reported from screening studies [1]. It is also likely that patients of both races with specific medical conditions (such as inflammatory disorders and liver disease) or African-Americans with certain symptoms occurring in MM (such as severe low back pain, severe bone pain, and/or repeated infections) but no diagnosis of MM may be more likely to undergo testing with serum protein electrophoresis. The use of a retrospective cohort rather than a prospective cohort study design could have potentially caused under-ascertainment of MM cases; however, the observed rates of 17% and 15% at 10 years are very similar to reported rates from the Mayo clinic [2] suggesting that most MM cases were identified in this study.

Our finding of a 3-fold higher prevalence of MGUS in African-Americans than in Whites, along with a similar cumulative probability of MM occurring subsequent to MGUS in both races, suggests that identification of etiologic factors of MGUS may be key to understanding factors that contribute to the racial disparity for MM. We conclude that the focus of epidemiological research on MM should be shifted to studies examining postulated risk factors for MGUS in order to understand the etiology of MM.

## AUTHOR INFORMATION

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**Author Contributions:** O Landgren and G Gridley designed the study and obtained data. O Landgren, G Gridley, and T R Fears analyzed data. O Landgren, G Gridley, I Turesson, N E Caporaso, L R Goldin, D Baris, T R Fears, R N Hoover and M S Linet were involved in the interpretation of the results. O Landgren initiated this work and wrote the report. All authors read, gave comments, and approved the final version of the manuscript. O Landgren, G Gridley, and T R Fears had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

**Conflict of Interest Statement:** We declare that we have no conflict of interest.

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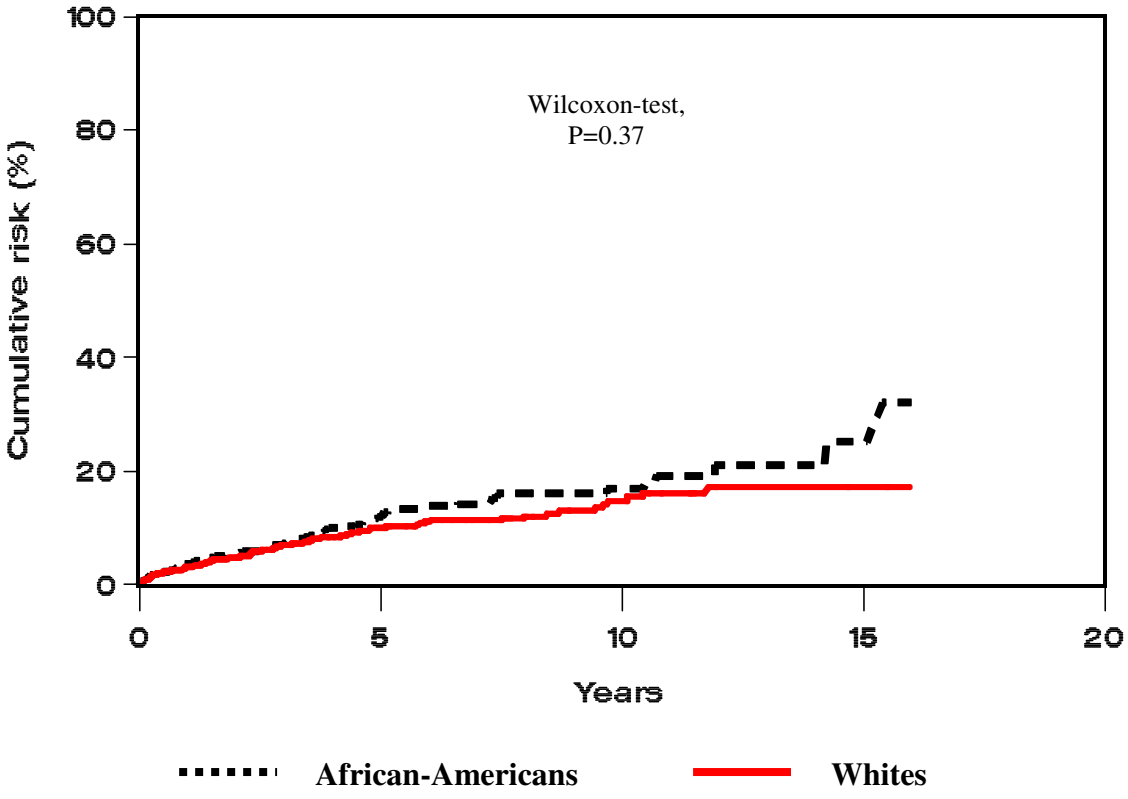
**TABLE 1. Characteristics of the study cohort (US Veterans Affairs): White and African-American male veterans with at least one hospital admission between October 1, 1980 and September 30, 1996, who were followed more than one year** [a]

| | Whites | | African-Americans | |
|---|---|---|---|---|
| **Characteristics** | **other than MGUS** | **MGUS** | **other than MGUS** | **MGUS** |
| Number of subjects | 3,248,795 | 1,312 | 749,020 | 734 |
| Mean age at study entry [b] | 53.8 | 63.7 | 49.4 | 61.5 |
| Years of follow-up (mean) [a] | 10.0 | 4.2 | 10.0 | 4.4 |
| Person years at risk [a] | 32,347,635 | 5,557 | 7,519,478 | 3,226 |
| Mean age at ascertainment of MGUS | | 68.3 | | 66.2 |
| Mean age at diagnosis of MM | 68.2 | 69.5 | 66.5 | 67.5 |
| Number of MM cases | 2,217 | 105 | 1,150 | 74 |
| Median number of hospital visits | 3 | 9 | 3 | 8 |

Abbreviations: MGUS=monoclonal gammopathy of undetermined significance.
MM=multiple myeloma.
[a] The first year of follow-up was censored.
[b] Age at first discharge record for inpatient hospitalization at Veterans Affairs hospitals between October 1, 1980 and September 30, 1996.

## FIGURE LEGENDS

**FIGURE 1. Cumulative risk of a subsequent diagnosis of multiple myeloma in the absence of other causes of death among African-American (n=734) and White (n=1,312) U.S. veterans with a previous history of monoclonal gammopathy of undetermined significance (MGUS)[a]**




[a] The cumulative risk was computed as 1.00 minus the Kaplan-Meier estimate